PATENT
Attorney Docket No.: 15270J-004766US

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	Confirmation No. 3041
Dale B. Schenk et al.	Examiner: Daniel E. Kolker
Application No.: 10/777,792	Technology Center/Art Unit: 1649
Filed: February 11, 2004	
For: PREVENTION AND TREATMENT OF AMYLOIDOGENIC DISEASE	REPLY BRIEF UNDER 37 C.F.R. § 41.41
Customer No.: 20350	

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Commissioner for Patents
P.O. Box 1450
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Sir:

This Reply Brief is submitted in response to the Examiner's Answer mailed October 27, 2009.

STATUS OF CLAIMS

Claims 1-118 are cancelled. Claims 119-143 are rejected.

GROUNDS OF REJECTION

1. Whether claims 119, 121-125, and 131 would have been obvious over Selkoe (US 5,262,332) [Selkoe], Wong, PNAS 82,8729-8732 (1985) [Wong] and Penney, US 5,773,007 [Penney].

2. Whether claims 119-125 and 131-132 would have been obvious over Selkoe, Wong, and Penney in further view of Restifo, US 5,733,548 [Restifo].

3. Whether claims 119, 121-125, 131 and 133-138 would have been obvious over Selkoe, Wong and Penney in further view of Hancock, US 5,723,130 [Hancock].

4. Whether claims 119, 121-131 and 133-143 would have been obvious over Selkoe, Wong, Penney and Hancock in further view of Collier, US 5,601,827 [Collier].

ARGUMENT

Page 3 to page 7, first paragraph of the Examiner's answer essentially repeat the Examiner's remarks from the final office action, for which no further comment by appellant is needed.

Page 7, second paragraph to page 12 of the Examiner's answer provide the Examiner's comments on the appeal brief and will be addressed in this reply. Most of the Examiner's comments are applicable to all four grounds of rejection. Although the Examiner divides these remarks into four main sections (A-D), sections A and C both concern the *prima facie* case and will be addressed together by appellant followed by sections B (unexpected results) and D (case law). Appellant then briefly comments on additional grounds of patentability applicable to claims 133-135, which are separately rejected under the third ground of rejection above.

1. *Prima Facie* Case Not Established

The disagreement between the Examiner and appellant as to whether a *prima facie* case of obviousness has been established can be approximately reduced to three issues. First, the Examiner views Selkoe's comment that some fragments of about 8 or more amino acids from Aβ are capable of producing antibodies (col. 4, lines 18-24) as motivation for the artisan to have used a fragment of only seven amino acids. In appellant's submission, a fair reading of Selkoe's comment that some fragments of about 8 or more residues can be used for generating antibodies is that a fragment of 8 residues is about the minimum size and that if a smaller fragment is used there is at least a risk of failure. There is no apparent reason that the artisan would have felt compelled to test the limits of fragment size and risk possible failure in generating an antibody rather than following the protocol of Wong (who used an Aβ1-10 fragment) or Selkoe who used an Aβ1-28 fragment. Common sense suggests such possible failure would have appeared to involve an unnecessary risk that in the absence of compensating benefit the artisan would have chosen to avoid. Thus, Selkoe provided no or insufficient reason for the artisan to have used a fragment of Aβ having only seven amino acids.

Second, even if contrary, to appellant's position, Selkoe were construed as having motivated selection of a peptide containing only seven amino acids, the art as a whole did not teach that those seven amino acids should be the first seven amino acids of the Aβ peptide as distinct from any other seven amino acids within the Aβ sequence of about 42 amino acids. As discussed in detail in the appeal brief (p. 11 and p. 12, first two paragraphs), neither Wong nor Selkoe provided any indication that an antibody binding to an epitope within residues 1-7 would have any advantages relative to an antibody binding to any other part of Aβ. In fact, as acknowledged by the Examiner (Answer at p. 9, second paragraph) Selkoe teaches that antibodies raised against amyloid plaques rather than short peptides are superior for this purpose.

Third, the Examiner views the KLH carrier discussed by Wong and the toxoid from a pathogenic bacteria of the present claims as having "slight differences," but does not take into account what these differences are in alleging *prima facie* obviousness (Answer at paragraph bridging pp. 7-8). As discussed in the appeal brief, the Penney reference cited by the Examiner teaches that Penney teaches that KLH is a preferred carrier for animal use (*see, e.g.*, col. 5, lines

2-4) whereas toxoids from pathogenic bacteria are suitable and commonly used for human use (*see, e.g.*, col. 2, lines 5-8; col. 5, lines 4-12). It would not have been obvious to replace Wong's use of KLH in animals with a toxoid from a pathogenic bacteria because Penney teaches that Wong was already using the preferred carrier for animal use (*see, e.g.*, col. 5, lines 2-4). Wong provides no indication of a potential human use that would have suggested any compensating benefit for foregoing the preferred carrier for animal use in favor of a toxoid from a pathogenic bacteria, taught by Penney as being suitable for human use. Without any indication of a human use by Wong, the purported switch from KLH to a toxoid from a pathogenic bacterium appears not to reflect the common sense approach of the artisan but instead an impermissible hindsight reconstruction of the claimed invention.

In sum, it is submitted that a *prima facie* case has not been established against any of the claims because (1) the art provided no or insufficient reason for the artisan to have used a fragment of Aβ of only seven amino acids, (2) the art did not provide any reason that these seven amino acids should correspond to Aβ1-7 and (3) the purported switch from a preferred carrier for use in animals to a carrier suitable for use in humans without any proposal of human use represents hindsight rather than the common sense approach of the artisan.

2. Unexpected Results

The appeal brief described two unexpected results of the claimed conjugate vis-a-vis the conjugate of Wong. First, the claimed conjugate is an unexpectedly superior agent for human therapeutic administration than the Aβ1-10-KLH-conjugate discussed by Wong because toxoid from a pathogenic bacterium is more suitable for human use whereas KLH is a preferred carrier for animal use (*see* Penney, col. 2, lines 5-8; and col. 5, lines 4-12). Second, the claimed conjugates are also unexpectedly advantageous for therapeutic use relative to Wong's Aβ1-10 fragment because the claimed use of Aβ1-7 preserves three epitopes predominantly responsible for plaque clearing effects, but reduces the likelihood of T-cell mediated side effects (Appeal Brief at p. 11 last paragraph and p. 12, first paragraph).

The Examiner disagrees with appellant's position regarding unexpected results for two reasons. First, the Examiner alleges that appellant is arguing advantages relative to the use

of a product rather than the product itself (Answer at p. 8 last paragraph, p. 9, last paragraph, and paragraph bridging pp. 10-11). However, advantages of a product in use are relevant to the product itself when the advantages stem directly from the product. "[A]dvantages...do not properly belong in the claims, the sole function of which is to point out distinctly the process, machine, manufacture or composition of matter which is patented...not its advantages.. It is entirely proper, nevertheless, in evaluating nonobviousness...to take into account advantages directly flowing from the invention patented." *Preemption Devices v. Minnesota Mining & Manufacturing Co.*, 732 F.2d 903, 907 (Fed. Cir. 1984). Here, the unexpected advantages mentioned above do flow directly from structural features of the claimed product. The first mentioned advantages flows directly from the selection of a toxoid from a pathogenic bacteria rather than KLH as a carrier. The second mentioned advantage flows from the lack of amino acids 8-10 in the claimed conjugate vis-a-vis the conjugate of Wong. Although both the claimed conjugate and the conjugate of Wong can each generate the three classes of antibodies indicated to be particularly useful by the data in Table 16 of the application (*see* appeal brief at p. 13, first paragraph), the conjugate of Wong has three extra amino acids not needed for generating these classes of antibodies, but which increase the possibility of T-cell mediated side effects (id.).

Second, the Examiner alleges that no evidence of superior therapeutic effects of the claimed conjugates for human administration vis-a-vis that of Wong has been provided (Answer at p. 9, first paragraph, paragraph bridging pp. 10-11). Although direct evidence in the form of a side-by-side comparison in a clinical trial has not been provided, appellant has provided indirect evidence that reasonably supports its position that the claimed conjugates have unexpectedly superior properties vis-a-vis that of Wong (*see* appeal brief at pp. 12, last paragraph and p. 13, first paragraph).

Briefly to recap, the evidence that the claimed conjugates are superior to Wong's conjugate for human use is based on the disclosure in Penney that a toxoid from a pathogenic bacterium is more suitable for human use whereas KLH is a preferred carrier for animal use (*see* Penney, col. 2, lines 5-8; and col. 5, lines 4-12). Although the advantage of toxoids from pathogenic bacteria for human use is not itself unexpected having already been reported by Penney, the advantage of the claimed conjugates is unexpected because the cited art did not teach

that the claimed conjugates had any use in humans. Without the insight provided by the present application that the claimed conjugates have a therapeutic use in humans, the claimed conjugates would have appeared disadvantageous relative to those of the art because the art was already using the preferred carrier for animal use. The advantageous property of the claimed conjugates for use in humans vis-a-vis the cited art can only be viewed as unexpected.

The unexpected advantage of the claimed conjugates vis-a-vis Wong related to use of a 1-7 fragment compared with a 1-10 fragment is supported by three pieces of evidence. First, the specification shows that three epitopes predominantly responsible for plaque clearing effects occur within residues 1-7 of Aβ (Table 16 of specification). Second, the art has reported minimum T-cell epitope size of about 9 amino acids (Rammensee, *Curr. Opin. Immunol.*, 1995, 7:85-96 at p. 89, paragraph bridging cols. 1-2). Third, post filing clinical trials have indicated a side effect in a small proportion of patients receiving unconjugated Aβ (residues 1-42) is likely mediated by T-cells (Gilman et al., *Neurology*, 64:1553-1562 (2005) at p. 1561, second col., 2nd paragraph; Greenberg et al., *Nature Medicine,* 9(4):389-390 (2003), at paragraph bridging 389-390; as well as references cited in appeal brief at p. 13, first paragraph of appeal brief) . In the aggregate, these reports provide evidence that an Aβ1-7 fragment is likely to be equally effective as an Aβ1-10 fragment in inducing three classes of antibodies primarily responsible for plaque clearing but even less likely to have T-cell mediated side effects because of its smaller size relative to the approximate minimum size of T-cell epitopes reported by Rammensee. This evidence supports the teaching of reduced side effects disclosed in the specification (*see* p. 13, first paragraph).

Thus, in appellant's submission, patentability of the present claims is supported by unexpected results reasonably based on evidence of record and flowing directly from the structures of products claimed.

3. Case Law

The appeal brief discussed distinctions over *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 82 USPQ2d 1321 (Fed. Cir. 2007) and *Alza Corp. v. Mylan Laboratories, Inc.*, 461 F.3d 1286, 80 USPQ2d 1001 (Fed. Cir. 2006) (appeal brief at p. 13, last paragraph to p. 15, first

paragraph). The Examiner's answer continues to allege that these cases are analogous in involving selection of an auxiliary agent to accompany a known product (Answer at pp. 9-10). However, the Examiner does not address a key distinction between the present facts and those of the cases. That is, the cases addressed selection of auxiliary agents for known drugs. By contrast, Aβ1-7 was not known to have any therapeutic properties. That it might be obvious to select alternative auxiliary agents to facilitate the same use of a known drug does not mean it would have been obvious to select an auxiliary agent to facilitate a new use of molecule before the new use was known. A similar distinction applies vis-a-vis *Merck & Co. v. Biocraft Laboratories*, 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir. 1989), which involved selecting a combination of two known drugs. That it might sometimes be obvious to combine two known drugs, likewise does not mean it would have been obvious to select an auxiliary agent to facilitate a use of molecule as a drug before the use as a drug was known.

4. Additional Distinctions for Claims 133-135

The above claims specify a QS-21 adjuvant in distinction from the Freund's adjuvant used by the art. As discussed in the appeal brief and not contested by the Examiner's answer, whereas QS-21 is suitable for administration to humans, Freund's adjuvant is the most commonly used adjuvant for animal use but is not routinely administered to humans because of toxicity. The Examiner nevertheless takes the view that because both QS-21 and Freund's adjuvant both stimulate immune responses, it would have been obvious to replace Freund's adjuvant in Wong with QS-21.

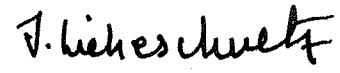
In appellant's submission, this purported replacement reflects impermissible hindsight rather than the common sense approach of the artisan. The art did not provide any reason to replace the most common adjuvant used in animals with an adjuvant suitable for human use but of unknown potency relative to Freund's adjuvant for use in animals. Furthermore, the replacement of Freund's adjuvant with QS-21 confers an unexpected benefit for use in humans The benefit in humans is unexpected not because QS-21's suitability for use in humans was unknown (this being reported by Hancock) but because Aβ1-7 was not known to

have any therapeutic use in humans. The claimed composition including QS-21, has a new and unexpected use, *i.e.*, therapeutic use in humans, for which Wong's composition was not suitable.

5. Conclusion

For these reasons, as well as the reasons provided in the appeal brief, it is respectfully submitted that the outstanding rejections should be reversed.

Respectfully submitted,



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Supplemental Evidence Appendix

Gilman et al., *Neurology*, 64:1553-1562 (2005), cited by information disclosure statement filed October 30, 2007 as cite no. 902, entered by office action of April 03, 2008.

Greenberg et al., *Nature Medicine*, 9(4):389-390 (2003), cited by information disclosure statement filed February 06, 2007 as cite no. 605, entered by office action of May 08, 2007.